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Assessing Exposure and Health Consequences of Chemicals in Drinking Water: Current State of Knowledge and Research Needs

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Abstract

Background: Safe drinking water is essential for wellbeing. Although microbiological contamination remains the largest cause of water-related morbidity and mortality globally, chemicals in water supplies may also cause disease, and evidence of the human health consequences is limited or lacking for many of them.

Objectives: We aimed to summarize the state of knowledge, identify gaps in understanding, and provide recommendations for epidemiological research relating to chemicals occurring in drinking water.

Discussion: The assessment of exposure and the health consequences of chemicals in drinking water is challenging. Exposures are typically at low concentrations, measurements in water are frequently insufficient, chemicals are present in mixtures, exposure periods are usually long, multiple exposure routes may be involved, and valid biomarkers reflecting the relevant exposure period are scarce. In addition, the magnitude of the relative risks tends to be small.

Conclusions: Research should include well designed epidemiological studies covering regions with contrasting contaminant levels and sufficient sample size; comprehensive evaluation of contaminant occurrence in combination with bioassays integrating the effect of complex mixtures; sufficient numbers of measurements in water to evaluate geographical and temporal variability; detailed information on personal habits resulting in exposure (e.g., ingestion, showering, swimming, diet); collection of biological samples to measure relevant biomarkers; and advanced statistical models to estimate exposure and relative risks, considering methods to address measurement error. Lastly, the incorporation of molecular markers of early biological effects and genetic susceptibility is essential to understand the mechanisms of action. There is a

particular knowledge gap and need to evaluate human exposure and risks of a wide range of emerging contaminants.

Introduction

The safety of water supplies is of paramount public health importance. It is estimated that 13% of the world population lacked access to improved drinking water sources in 2008 (UNICEF and WHO 2011) and that almost 10% of the total burden of disease worldwide could be prevented by improving drinking water supply, sanitation, hygiene, and management of water resources (Prüss-Üstün et al. 2008). Microbiological contamination is the largest cause of waterborne disease at a global scale. However, chemicals in water supplies can be related to health risks, generally when associated with long-term exposures (Thompson et al. 2007).

There are uncertainties about the safety of current standards for some regulated chemicals, and the potential health impacts of unregulated or emerging chemical contaminants are largely unknown. In May 2012, a workshop was held in the Centre for Research of Environmental Epidemiology (CREAL), Barcelona, Spain, with the aim of advancing the field of epidemiology and chemical contaminants in water and to make recommendations for future research. Our suggestions aspire to be useful and applicable to any type of chemical contaminant occurring in drinking water. Chemicals that we discuss as examples in this manuscript are substances whose main pathway of human exposure is through drinking water. Although the chemical universe is broad and most chemicals do not occur exclusively in drinking water, water is essential for life and exposures to chemicals in drinking water, even at low concentrations, may have important consequences across the entire population. We focus on cancer as example, and summarize the main discussion points and conclusions of the workshop.

Occurrence

Regulated chemicals

Drinking water quality is regulated in most countries, and monitoring is conducted routinely. A complete list of chemicals that are currently regulated in drinking water, and the regulatory limits promulgated for each chemical by the World Health Organization (WHO 2011), the US Environmental Protection Agency (USEPA 2009), and the European Union (EU 1998) are provided in Table 1. These regulatory guidelines require periodic review to be updated according to new evidence. For example, the USEPA reduced its maximum contaminant level (MCL) for arsenic from 50 µg/l in 1942 to the current level of 10 µg/l in response to growing scientific evidence of adverse health effects (Smith et al. 2002). Epidemiological studies have reported associations of trihalomethane (THM) levels in drinking water (a surrogate measure of the disinfection by-product mixture) and bladder cancer (Villanueva et al. 2004) at THM levels lower than the current regulations in the US and the European Union (80 and 100 µg/l, respectively, Table 1). The current MCL for nitrate was set based on methemoglobinemia among infants, but there is uncertainty concerning the safety of this MCL for chronic effects over longer exposure periods (e.g., on cancer) (Ward et al. 2005). Manganese is a neurotoxin associated to learning disabilities and deficits in intellectual function in children (Zoni and Lucchini 2013). The manganese guideline by the WHO has been fluctuating from initially 500 µg/L in 1958 (Ljung and Vahter 2007) to the discontinuation in the current 4th edition of the WHO guidelines (WHO 2011). This has generated controversy in the scientific community, as the previous guideline before discontinuation (400 µg/l) was questionable by some authors (Ljung and Vahter 2007) and the discontinuation has received criticisms (Frisbie et al. 2012). Although many contaminants are monitored and regulated, the adequacy of the MCL approach is open to debate,

in part because these limits are often based on animal-based toxicological studies, since human studies are not available or inconclusive.

Emerging chemical contaminants

Non-regulated chemicals are of particular concern and constitute a main focus of current research (Richardson and Ternes 2011). Wastewater from human activities may contaminate water supply sources with pharmaceuticals, nanoparticles, consumer products (such as sunscreens), and other contaminants (Table 2), and these chemicals have been identified in drinking water (Ternes 2007). For example, iodinated or nitrogenated disinfection by-products (DBPs), which are unregulated DBPs that are more toxic than their chlorinated and carbonaceous DBP analogues (Plewa et al. 2008b), may occur in water supplies at very low concentrations (Plewa et al. 2004; Plewa et al. 2008a). Degradation by-products of pharmaceuticals, which may be more toxic than their parent compounds, also have been identified in drinking water (Shen and Andrews 2011). The contribution of drinking water as a source of exposure to perfluorinated chemicals may be as important as dietary intake (Ericson et al. 2008), and evidence suggests that continued human exposure to even relatively low concentrations of PFOA in drinking water results in elevated body burdens that may increase the risk of health effects (Post et al. 2012). Although concentrations are generally low (usually in the range of nanograms/liter) and some individual chemicals may pose no appreciable risks to human health (Schriks et al. 2010), there are concerns about potential risks of exposures to mixtures (Silva et al. 2002). The removal efficiency by drinking water treatment processes has been evaluated for some substances (WHO 2012) but is poorly known for many emerging pollutants.

Global Indicators of Toxicity

Water supplies often include mixtures of chemical contaminants that vary in time and space. However, the epidemiological and toxicological evaluation of mixtures involves significant challenges, in many cases beyond the limits of current research methods. *In vitro* bioassays (or biosensors) developed by toxicological research are promising tools for measuring the global toxicity of chemical mixtures in water samples that may be coupled with more in-depth analysis of specific contaminants when a positive response is detected. For example, Jeong et al. (2012) evaluated *in vitro* mammalian cell toxicity for a range of DBPs in an attempt to identify specific DBPs responsible for genomic DNA damage (Jeong et al. 2012). Endpoints that can be measured by *in vitro* bioassays include mutagenicity (Ames test) (Richardson et al. 2010), genotoxicity (micronuclei, Comet assay) (Plewa et al. 2010), endocrine disruption (DR-CALUX bioassay) (Brand et al. 2013; Sato et al. 2010), and cytotoxicity (Plewa et al. 2010). Although the use of these markers is not without limitations (such as complex and non-standardized sample pretreatment methods needed to obtain concentrates before laboratory analysis, uncertain validity for some of the assays, limited throughput development, elevated cost, low sensitivity, and results reflecting only short-term exposure evaluations), further development of these techniques and their incorporation into epidemiological research may improve understanding of the effects of mixtures. These efforts will require improved communication and collaboration among scientific disciplines, including analytical chemists, toxicologists, and epidemiologists.

Human Exposure

Accurate exposure assessment in human observational studies is essential to obtain valid results and constitutes a main methodological challenge, as summarized in Table 3. Difficulties in

identifying and measuring contaminants in water supplies at very low concentrations and substances occurring in mixtures hamper the evaluation of human exposure, requiring new methods in health risk analysis (Schwarzenbach et al. 2006).

Disinfection by-products (DBPs) are an example of chemicals occurring in complex mixtures, and this has been addressed in part by using a few compounds as surrogates for the DBP mixture as a whole. For example, observational studies of human DBP exposures and health effects have focused on a small subset of the several hundred DBPs that may occur in public water supplies (Richardson et al. 2007), particularly the trihalomethanes (THMs) and haloacetic acids (HAAs) (Hinckley et al. 2005; Hoffman et al. 2008; Righi et al. 2012). However, although these compounds are often used as a surrogate for other DBPs, the assumption that they correlate with other DBPs is not universally supported and correlations can vary in time and space (Villanueva et al. 2012).

Methods of exposure assessment are influenced by the specific outcome under study. For instance, for endpoints with long latency such as cancer, long time periods over several decades need to be evaluated. While for reproductive outcomes, it is very important to accurately capture the temporal variation in exposure over a shorter period covering the relevant time windows before and during gestation.

Chemicals or metabolites have been measured in biological samples in epidemiological studies to estimate exposures, e.g., urinary or toenail arsenic measurements in cancer studies (Karagas et al. 2004). Urine trichloroacetic acid is a promising biomarker of DBPs that requires methodological development prior to a generalized use in epidemiological studies (Savitz 2012). In addition, among the available biomarkers specific for drinking water contaminants, many have

short half-lives (e.g., urinary trichloroacetic acid) and are thus of limited value to associate with health outcomes that require long-term exposures (Savitz 2012). Consequently, exposure assessment in most instances relies on assessment of personal behavior ascertained through questionnaires and measurement of environmental levels (Hoffman et al. 2008; Levallois et al. 2012).

Inhalation and dermal contact may be relevant exposure routes for volatile or skin-permeable chemicals. In such case, activities involving different water uses at home (e.g., showering, bathing), in recreation (e.g., swimming in pools), and through occupations involving water contact should be considered.

Alternative methods of exposure assessment may involve statistical modeling, such as models based on known geographic distributions of contaminants (Toledano et al. 2005), hydrological modeling of underground plumes of contaminants (Gallagher et al. 2010), and/or surrogate parameters such as land use (Aschebrook-Kilfoy et al. 2012). Several methods can be used in combination, tailored to the availability of data, such as in a recent study on the long-term exposure to arsenic and cancer (Nuckols et al. 2011), that combine arsenic data from own measurements in water samples collected at home of participants, data from public water utilities and historical data for aquifers.

Exposure estimates with minimal measurement error are necessary to produce valid effect estimates. Misclassification of exposure is of particular concern at the low exposure range, as it tends, under most scenarios, to attenuate associations towards the null (Cantor and Lubin 2007; Waller et al. 2001) or reduce the precision of associations (Wright and Bateson 2004). Strategies to minimize measurement error are necessary from study design to data analysis, and include for

example the collection of repeated measures of individual water use over the relevant exposure period (Forssen et al. 2009) and assessing reliability of interviews to exclude unreliable questionnaires (Villanueva et al. 2009).

Health Effects

The following is an overview of epidemiological findings from individual-based studies of chemical contaminants in water and cancer. Table 4 displays a summary of the evidence of carcinogenicity as evaluated and concluded by the WHO International Agency for Research on Cancer (IARC).

There is sufficient evidence in humans that arsenic in drinking water causes cancers of the urinary bladder, lung and skin (IARC 2004). Studies conducted in areas with lower levels of arsenic in drinking water (at or below the MCL) have reported inconsistent results, and cancer risks associated with exposure to low arsenic levels over decades remain uncertain.

Bladder cancer has been consistently associated with DBP exposure (Cantor 2010), and pooled analyses combining data from studies conducted in different countries have reported associations between bladder cancer and THM at levels below current MCLs (Costet et al. 2011; Villanueva et al. 2004). Some (King et al. 2000; Cragle et al. 1985; Wilkins and Comstock 1981) but not all (Hildesheim et al. 1998; Koivusalo et al. 1997; Doyle et al. 1997) studies of DBP exposure and colon cancer have reported positive associations. Similarly, positive associations for DBP exposure have been found for rectal cancer (Bove, Jr. et al. 2007; Hildesheim et al. 1998; Doyle et al. 1997), not replicated in other studies (King et al. 2000; Koivusalo et al. 1997; Wilkins and Comstock 1981).

The epidemiological investigation for nitrate and cancer has been challenging. Drinking water may be a primary source of nitrate exposure when drinking water concentrations are above 50 mg/L (IARC 2010). Below this threshold, diet is the main exposure route, involving complex mechanisms of action through endogenous formation of N-nitroso compounds (IARC 2010). Long-term exposure to nitrate in drinking water has been evaluated in relation to multiple cancer sites including esophagus, stomach, bladder, and colon (IARC 2010). Although there is inadequate human evidence for carcinogenicity, there is sufficient evidence from experimental animals for the carcinogenicity of nitrite in combination with amines or amides, and ingested nitrate under conditions that result in endogenous nitrosation has been classified as probably carcinogenic to humans (IARC 2010).

Other contaminants have been less extensively investigated in relation to cancer risk. Fluoride is added to drinking water at low concentrations in some countries to prevent dental caries, and naturally occurs in water at higher levels in certain parts of the world such as the Rift Valley in Africa (Malde et al. 2011). The IARC evaluated fluoride carcinogenicity in 1987 (IARC 1987) and concluded that human and animal evidence was inadequate (Table 3). Some epidemiological studies on osteosarcoma have been published after this evaluation (Bassin et al. 2006; Kim et al. 2011) but consistent associations are not observed.

The liver is a target organ for microcystin-LR (IARC 2010), which are toxins produced from cyanobacteria resulting from algae blooms and the eutrophication of surface waters. Individual-based studies evaluated by the IARC (two cohort and four case-control studies) have assessed exposure by comparing water consumed in pond or ditches vs. other sources and no measurements of toxins or bacteria are considered. In consequence, the IARC concluded that evidence in humans for the carcinogenicity of microcystin-LR is inadequate (IARC 2010). Other

carcinogens such as heavy metals, pesticides, and solvents may occur in drinking water as a consequence of human activities and natural hydrogeochemical processes. However, evidence on the cancer risk on human populations is limited.

Mechanisms and Biomarkers

The elucidation of mechanisms of action to provide biological plausibility and support causality suggested by epidemiological associations is a priority in current research. Biomarkers of early effect can be used in epidemiological studies to provide evidence about subclinical or intermediate effects of exposures (e.g., cytogenetic changes), effects of very low exposure levels, and can be used in experimental studies to evaluate the effect of an intervention. For an intermediate biomarker to be informative it should be associated with both the disease and exposure of interest, and reflect an intermediate step in the pathway between exposure and disease. For example, a suggested mechanism of action for arsenic is through epigenetic dysregulation, although there are limited human studies available (Ren et al. 2011). In addition, the evaluation of genetic variants may be used to identify susceptible populations underlying the biological mechanisms of action. For example, the evaluation of genetic variants of DBP metabolizing enzymes in an epidemiological study on bladder cancer and THM exposure has shown that polymorphisms in key metabolizing enzymes modified DBP-associated bladder cancer risk (Cantor et al. 2010). In addition, the consistency of these findings with experimental observations of GSTT1, GSTZ1, and CYP2E1 activity strengthens the hypothesis that DBPs cause bladder cancer and suggests possible mechanisms as well as the classes of compounds likely to be implicated (Cantor et al. 2010). There are few validated biomarkers specific for chemical contaminants in drinking water. However, the availability of prospective studies with bio-banked samples and biotechnological development allowing large numbers of compounds to

be measured in small amounts of biological samples (urine, plasma, serum) is encouraging. These technologies include genomics, epigenomics, transcriptomics, adductomics, proteomics and metabolomics (Rappaport and Smith 2010; Wild 2005). Application of these techniques will facilitate a comprehensive approach to identify perturbations in biological systems and associated mechanisms of action (Moore et al. 2013). These technologies have not been widely applied in water research but have shown promising results in other areas of environmental research.

Future Challenges

Climate change

A significant and growing body of evidence suggests that climate change will have a detrimental effect on the quality of water available for human consumption in the future. For example, increasing temperatures may enhance conditions for the proliferation of cyanobacteria and algae (Joehnk et al. 2008; Newcombe et al. 2012; Paerl and Huisman 2008). Cyanobacteria are of particular concern for human populations as they can produce cyanotoxins such as microcystin that have carcinogenic effects (IARC 2010). The frequency of extreme weather events is expected to increase as a consequence of climate change, and the concentrations of chemical contaminants may be affected by extreme precipitation events. For example, tests conducted in models of different types of soils showed that certain mobile pharmaceuticals occur at higher concentrations in soil and groundwater during and directly after intense precipitation events (Oppel et al. 2004). Simulation studies have shown that pesticide concentrations fluctuate with changes in precipitation intensity and seasonality (Probst et al. 2005; Bloomfield et al. 2006). Evidence concerning the effect of drought is mixed. For example, concentrations of heavy metals introduced primarily from anthropogenic activities (e.g., such as chrome, mercury, lead and

cadmium) in the Rhine River basin are higher during drought years (Zwolsman and van Bokhoven 2007). In contrast, no significant changes during drought conditions, but significant variability between seasons, has been described in the Dommel River, a tributary of the Meuse river in the Netherlands, as increased groundwater flow in winter led to increased metal concentrations (Wilbers et al. 2009). In summary, it is expected that climate change could adversely affect drinking water quality but there is limited knowledge about the magnitude and distribution of the impact at different scales (global, regional, local).

Final Remarks and Recommendations

General aspects

Although microbiological contamination is the largest contribution to waterborne disease and mortality at a global scale, chemical contaminants in water supplies also can cause disease, sometimes after long periods of exposure. The concentrations in drinking water, the prevalence of human exposure in the population, and the level of toxicity can be used to prioritize chemicals for further research. These characteristics may vary geographically and therefore further research should be designed to local, regional, or country specific circumstances as appropriate. Finally, exposures and risks affecting vulnerable populations (e.g., pregnant women and children) require special attention and are of particular interest.

Arsenic is a unique example of a substance in drinking water with conclusive evidence from human epidemiological studies. There is no doubt that arsenic is a human carcinogen at high concentrations (IARC 2004), but there is inadequate information to determine the carcinogenic potential of other chemicals that occur in drinking water (Table 4). Unique characteristics of arsenic include the fact that drinking water represents the predominant source of exposure in the

population, the levels in water and thus the magnitude of the exposure is very high in certain areas (e.g., Bangladesh), the availability of measurements in drinking water has allowed the development of epidemiological studies, the wide variability in exposures facilitates the detection of risks, the occurrence as an isolated substance rather than in mixtures allows the direct measurement of the putative agent, the magnitude of the risks are high compared to other chemicals, and the existence of biomarkers has helped to improve exposure assessment and elucidation of mechanisms of action.

On occurrence and exposure assessment

Improved exposure assessment to water contaminants is essential to derive valid exposure-response curves and useful knowledge for risk assessment and regulation, and here we provide some suggestions.

- The research need concerning regulated chemicals is to clarify the effects at or below the MCL, which are suspected for some contaminants. Access to water utility monitoring data, which is necessary to conduct such studies, should be encouraged and facilitated. Access to large databases would facilitate improved exposure assessment in epidemiological studies, if the data are reliable and sufficient to evaluate temporal and geographical variations applicable to study areas.
- The measurement of emerging contaminants needs advanced and specialized analytical methods, and close collaboration between epidemiologists and analytical chemists is required to provide contaminant occurrence data that is suitable in format and quantity for epidemiological research. Better communication between epidemiologists and environmental analytical chemists would facilitate human health studies in this area. A mechanism to converge interests might be to collect water samples for analytical chemistry method

development alongside on-going epidemiological studies, or training analytical chemists in exposure assessment.

- The evaluation of mixtures requires some attention in future studies. It remains a challenge beyond current methods, and new developments may contribute to understand the health effects of chemical contaminants in drinking water.
- Some *in vitro* assays as indicators of water toxicity are promising tools deserving to be incorporated in future studies to complement exposure assessment and health risk analyses. These bioassays may be especially effective to evaluate the global effect of chemical mixtures and identify ‘hot spots’ of toxicity. In addition, such findings can be useful to generate hypothesis for more in-depth and resource-intensive analysis of specific contaminants and health outcomes. The incorporation of these methods in epidemiological research should be encouraged, and further validation should be conducted when necessary.
- Epidemiological research generally requires large numbers of measurements and data. This may constitute a challenge in the collaboration with analytical chemists and toxicologists if experimental methods are manual or laborious, and should be overcome in the future, e.g., with the development of high-throughput techniques able to analyze large amounts of water samples.
- On-going cohort studies should be encouraged to incorporate a water dimension, since retrospective assessment is challenging particularly for outcomes with long latency (e.g., cancer). This would require water sample collection, measurements, and personal questionnaires in on-going cohort studies, and new or reinforced collaborations between research groups. New cohorts (or data collections in existing cohorts) should be also

encouraged to implement environmental sampling and storage of such samples (Envirobanking) for use in future nested case-control studies.

- Methods developed for environmental and geospatial sciences, including geographical information systems and fate/transport modeling of chemicals, have been demonstrated to be useful in exposure assessment for risk analysis for waterborne chemical contaminants. Consequently, greater emphasis to incorporate these methodologies into environmental epidemiological studies should be made.
- Climate change is likely to impact on water quality with uncertain implications on human health. Research to evaluate these impacts and the potential human health consequences at different regional scales and in different climates is necessary.

On epidemiological methods

Epidemiological studies based on rigorous study design are essential to properly evaluate the human health risks associated with chemical contaminants in drinking water. Here we summarize some suggestions in this direction:

- There is a need to investigate the potential health outcomes of emerging (non-regulated) contaminants because current knowledge on health effects is mainly limited to regulated chemicals. However, there are still uncertainties and further research is needed to evaluate potential effects below MCLs for certain regulated chemicals.
- Studies capturing widely contrasting exposure levels are particularly useful to estimate risks. For this reason, environmental epidemiologists should influence the decision as to the location of study sites on this basis.
- Large studies with sufficient statistical power are necessary when the expected health risks are small in magnitude. It is advisable to know contaminant levels and exposure prevalence

before undertaking an epidemiological study to allow the estimation of sample size to reach sufficient statistical power.

- The incorporation of biomarkers of exposure, effect, and genetic susceptibility in epidemiological studies is encouraged to identify molecular mechanisms of action and contribute to the assessment of causality. Studies evaluating biomarkers could be companion studies within ongoing larger studies or small-medium size experimental studies. In particular, -omic technologies can add to current understanding of biological mechanisms and generate new hypotheses, requiring advanced and complex statistical tools to deal with the large amounts of data generated. However, biomarkers must be validated and biomarker studies generally require large numbers of observations and replication in multiple populations. Additional drawbacks of biomarker studies are the relatively high cost, the limitation of biomarkers with regard to capturing past exposures, invasiveness and the possibility for reverse causation (i.e., in cross-sectional or case-control studies).

General conclusions

In summary, the assessment of the health impacts of chemical contaminants in drinking water is a challenge that requires improved methodologies and enhanced interdisciplinarity in future epidemiological studies. Useful and valuable knowledge will increase if future studies successfully integrate existing and new developments from analytical chemistry, toxicology, exposure science, molecular epidemiology, statistics, environmental epidemiology, environmental sciences, engineering, and geospatial sciences. Improved cooperation and collaboration with stakeholders such as the water industry, regulatory and public health agencies, and affected communities would serve to produce higher quality risk analyses, as well as improve the likelihood to implement effective and early intervention measures. Institutional

support promoting access to reliable routine monitoring data at all levels and collaboration with stakeholders (e.g., water utilities, regulators, and consumer groups) would be beneficial. Finally, research efforts in this area are frequently hampered by the lack of specific funding for this research field and the availability of stable and substantial financial support is needed, either from governmental and non-governmental sources.

References

- Aschebrook-Kilfoy B, Heltshe SL, Nuckols JR, Sabra MM, Shuldiner AR, Mitchell BD et al. 2012. Modeled nitrate levels in well water supplies and prevalence of abnormal thyroid conditions among the Old Order Amish in Pennsylvania. *Environ Health* 11:6.
- Bassin EB, Wypij D, Davis RB, Mittleman MA. 2006. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes Control* 17:421-428.
- Bloomfield JP, Williams RJ, Gooddy DC, Cape JN, Guha P. 2006. Impacts of climate change on the fate and behaviour of pesticides in surface and groundwater--A UK perspective. *Sci Total Environ* 369:163-177.
- Boas M, Feldt-Rasmussen U, Main KM. 2012. Thyroid effects of endocrine disrupting chemicals. *Mol Cell Endocrinol* 355:240-248.
- Bond T, Huang J, Templeton MR, Graham N. 2011. Occurrence and control of nitrogenous disinfection by-products in drinking water--a review. *Water Res* 45:4341-4354.
- Bove GE, Jr., Rogerson PA, Vena JE. 2007. Case control study of the geographic variability of exposure to disinfectant byproducts and risk for rectal cancer. *Int J Health Geogr* 6:18.
- Brand W, de Jongh CM, van der Linden SC, Mennes W, Puijker LM, van Leeuwen CJ et al. 2013. Trigger values for investigation of hormonal activity in drinking water and its sources using CALUX bioassays. *Environ Int* 55:109-118.
- Cantor KP. 2010. Carcinogens in drinking water: the epidemiologic evidence. *Rev Environ Health* 25:9-16.
- Cantor KP, Lubin JH. 2007. Arsenic, Internal Cancers, and Issues in Inference from Studies of Low Level Exposures in Human Populations. *Toxicol Appl Pharmacol* 222:252-257.
- Cantor KP, Villanueva CM, Silverman DT, Figueroa JD, Real FX, Garcia-Closas M et al. 2010. Polymorphisms in GSTT1, GSTZ1, and CYP2E1, disinfection by-products, and risk of bladder cancer in Spain. *Environ Health Perspect* 118:1545-1550.
- Costet N, Garlantezec R, Monfort C, Rouget F, Gagniere B, Chevrier C et al. 2012. Environmental and urinary markers of prenatal exposure to drinking water disinfection by-products, fetal growth, and duration of gestation in the PELAGIE birth cohort (Brittany, France, 2002-2006). *Am J Epidemiol* 175:263-275.

- Costet N, Villanueva CM, Jaakkola JJ, Kogevinas M, Cantor KP, King WD et al. 2011. Water disinfection by-products and bladder cancer: is there a European specificity? A pooled and meta-analysis of European case-control studies. *Occup Environ Med* 68:379-385.
- Cragle, D.L., Shy, C.M., Struba, R.J. and Siff, E.J.: 1985, A case-control study of colon cancer and water chlorination in North Carolina. In: Jolley R.L., Bull R.J., Davis W.P., Katz S., Roberts M.H.Jr. and Jakobs V.A. (eds.), *Water Chlorination: chemistry, environmental impact and health effects* Lewis Publishers, Inc., Chelsea, MI (USA), pp. 153-160.
- DeWitt JC, Peden-Adams MM, Keller JM, Germolec DR. 2012. Immunotoxicity of perfluorinated compounds: recent developments. *Toxicol Pathol* 40:300-311.
- Diaz-Cruz MS, Gago-Ferrero P, Llorca M, Barcelo D. 2012. Analysis of UV filters in tap water and other clean waters in Spain. *Anal Bioanal Chem* 402:2325-2333.
- Dingemans MM, van den BM, Westerink RH. 2011. Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environ Health Perspect* 119:900-907.
- Doyle TJ, Zheng W, Cerhan JR, Hong CP, Sellers TA, Kushi LH et al. 1997. The association of drinking water source and chlorination by-products with cancer incidence among postmenopausal women in Iowa: a prospective cohort study. *Am J Public Health* 87:1168-1176.
- Ericson Jogsten I. 2011. Assessment of human exposure to per- and polyfluorinated compounds (PFCs). Exposure through food, drinking water, house dust and indoor air. *Örebro Studies in Chemistry*. ISBN 978-91-7668-811-3. Available: <http://oru.diva-portal.org/smash/get/diva2:436643/FULLTEXT03> [accessed 26 July 2013]
- Ericson I, Nadal M, van Bavel B, Lindstrom G, Domingo JL. 2008. Levels of perfluorochemicals in water samples from Catalonia, Spain: is drinking water a significant contribution to human exposure? *Environ Sci Pollut Res Int* 15:614-619.
- EU (European Union) Council. 1998. COUNCIL DIRECTIVE 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Available: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF> [accessed 23 July 2013]

- Forssen UM, Wright JM, Herring AH, Savitz DA, Nieuwenhuijsen MJ, Murphy PA. 2009. Variability and predictors of changes in water use during pregnancy. *J Expo Sci Environ Epidemiol* 19:593-602.
- Frisbie SH, Mitchell EJ, Dustin H, Maynard DM, Sarkar B. 2012. World health organization discontinues its drinking-water guideline for manganese. *Environ Health Perspect* 120:775-778.
- Gallagher LG, Webster TF, Aschengrau A, Vieira VM. 2010. Using residential history and groundwater modeling to examine drinking water exposure and breast cancer. *Environ Health Perspect* 118:749-755.
- Hildesheim ME, Cantor KP, Lynch CF, Dosemeci M, Lubin J, Alavanja M et al. 1998. Drinking water source and chlorination byproducts. II. Risk of colon and rectal cancers. *Epidemiology* 9:29-35.
- Hinckley AF, Bachand AM, Reif JS. 2005. Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. *Environ Health Perspect* 113:1808-1813.
- Hoffman CS, Mendola P, Savitz DA, Herring AH, Loomis D, Hartmann KE et al. 2008. Drinking water disinfection by-product exposure and fetal growth. *Epidemiology* 19:729-737.
- Huerta-Fontela M, Galceran MT, Ventura F. 2008. Stimulatory drugs of abuse in surface waters and their removal in a conventional drinking water treatment plant. *Environ Sci Technol* 42:6809-6816.
- IARC (International Agency for Research on Cancer). 1987. Supplement 7. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, IARC Scientific Publications, Lyon, France. Available: <http://monographs.iarc.fr/ENG/Monographs/suppl7/> [accessed 26 July 2013]
- IARC (International Agency for Research on Cancer). 2004. Some drinking water disinfectants and contaminants, including arsenic. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol 84, IARC Scientific Publications, Lyon, France. Available: <http://monographs.iarc.fr/ENG/Monographs/vol84/mono84.pdf> [accessed 26 July 2013]

- IARC (International Agency for Research on Cancer). 2010. Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol 94., IARC Scientific Publications, Lyon, France. Available: <http://monographs.iarc.fr/ENG/Monographs/vol94/> [accessed 26 July 2013]
- Jeong CH, Wagner ED, Siebert VR, Anduri S, Richardson SD, Daiber EJ et al. 2012. Occurrence and Toxicity of Disinfection Byproducts in European Drinking Waters in Relation with the HIWATE Epidemiology Study. *Environ Sci Technol* 46:12120-12128.
- Joehnk KD, Huisman J, Sharples J, Sommeijer B, Visser PM, Stroom JM. 2008. Summer heatwaves promote blooms of harmful cyanobacteria. *Global change biology* 14:495-512.
- Karagas MR, Tosteson TD, Morris JS, Demidenko E, Mott LA, Heaney J et al. 2004. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. *Cancer Causes Control* 15:465-472.
- Kim FM, Hayes C, Williams PL, Whitford GM, Joshipura KJ, Hoover RN et al. 2011. An assessment of bone fluoride and osteosarcoma. *J Dent Res* 90:1171-1176.
- King WD, Marrett LD, Woolcott CG. 2000. Case-control study of colon and rectal cancers and chlorination by-products in treated water. *Cancer Epidemiol Biomarkers Prev* 9:813-818.
- Koivusalo M, Pukkala E, Vartiainen T, Jaakkola JJ, Hakulinen T. 1997. Drinking water chlorination and cancer-a historical cohort study in Finland. *Cancer Causes Control* 8:192-200.
- Levallois P, Gingras S, Marcoux S, Legay C, Catto C, Rodriguez M et al. 2012. Maternal exposure to drinking-water chlorination by-products and small-for-gestational-age neonates. *Epidemiology* 23:267-276.
- Ljung K, Vahter M. 2007. Time to re-evaluate the guideline value for manganese in drinking water? *Environ Health Perspect* 115:1533-1538.
- Malde MK, Scheidegger R, Julshamn K, Bader HP. 2011. Substance flow analysis: a case study of fluoride exposure through food and beverages in young children living in Ethiopia. *Environ Health Perspect* 119:579-584.
- Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS. 2010. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. *Environ Health Perspect* 118:686-692.

- Moore LE, Karami S, Steinmaus C, Cantor KP. 2013. Use of OMIC technologies to study arsenic exposure in human populations. *Environ Mol Mutagen* 54:589-595.
- Newcombe G, Chorus I, Falconer I, Lin TF. 2012. Cyanobacteria: impacts of climate change on occurrence, toxicity and water quality management. *Water Res* 46:1347-1348.
- Nuckols JR, Freeman LE, Lubin JH, Airola MS, Baris D, Ayotte JD et al. 2011. Estimating water supply arsenic levels in the New England Bladder Cancer Study. *Environ Health Perspect* 119:1279-1285.
- Oppel J, Broll G, Löffler D, Meller M, Rombke J, Ternes T. 2004. Leaching behaviour of pharmaceuticals in soil-testing-systems: a part of an environmental risk assessment for groundwater protection. *Sci Total Environ* 328:265-273.
- Paerl HW, Huisman J. 2008. Climate. Blooms like it hot. *Science* 320:57-58.
- Pham TP, Cho CW, Yun YS. 2010. Environmental fate and toxicity of ionic liquids: a review. *Water Res* 44:352-372.
- Plewa MJ, Muellner MG, Richardson SD, Fasano F, Buettner KM, Woo YT et al. 2008a. Occurrence, synthesis, and mammalian cell cytotoxicity and genotoxicity of haloacetamides: an emerging class of nitrogenous drinking water disinfection byproducts. *Environ Sci Technol* 42:955-961.
- Plewa MJ, Simmons JE, Richardson SD, Wagner ED. 2010. Mammalian cell cytotoxicity and genotoxicity of the haloacetic acids, a major class of drinking water disinfection by-products. *Environ Mol Mutagen* 51:871-878.
- Plewa, M.J., Wagner, E.D., Muellner, M.G., Hsu, K.M. and Richardson, S.D.: 2008b, Comparative mammalian cell toxicity of N-DBPs and C-DBPs. In: Karanfil T., Krasner S., Westerhoff P. and Xie Y. (eds.), *In Occurrence, formation, health effects and control of disinfection by-products in drinking water* American Chemical Society, Washington, D.C., pp. 36-50.
- Plewa MJ, Wagner ED, Richardson SD, Thurston AD, Woo YT, McKague AB. 2004. Chemical and biological characterization of newly discovered iodoacid drinking water disinfection byproducts. *Environ Sci Technol* 38:4713-4722.
- Post GB, Cohn PD, Cooper KR. 2012. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. *Environ Res* 116:93-117.

- Probst M, Berenzen N, Lentzen-Godding A, Schulz R. 2005. Scenario-based simulation of runoff-related pesticide entries into small streams on a landscape level. *Ecotoxicol Environ Saf* 62:145-159.
- Prüss-Üstün A., Bos R, Gore F. and Bartram J.: 2008, *Safer water, better health: costs, benefits and sustainability of interventions to protect and promote health*, Geneva. Available: http://whqlibdoc.who.int/publications/2008/9789241596435_eng.pdf [accessed 26 July 2013]
- Rappaport SM, Smith MT. 2010. Epidemiology. Environment and disease risks. *Science* 330:460-461.
- Ren X, McHale CM, Skibola CF, Smith AH, Smith MT, Zhang L. 2011. An emerging role for epigenetic dysregulation in arsenic toxicity and carcinogenesis. *Environ Health Perspect* 119:11-19.
- Richardson SD, DeMarini DM, Kogevinas M, Fernandez P, Marco E, Lourencetti C et al. 2010. What's in the Pool? A Comprehensive Identification of Disinfection By-Products and Assessment of Mutagenicity of Chlorinated and Brominated Swimming Pool Water. *Environ Health Perspect* 118:1523–1530.
- Richardson SD, Plewa MJ, Wagner ED, Schoeny R, DeMarini DM. 2007. Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: A review and roadmap for research. *Mutat Res* 636:178-242.
- Richardson SD, Ternes TA. 2011. Water analysis: emerging contaminants and current issues. *Anal Chem* 83:4614-4648.
- Righi E, Bechtold P, Tortorici D, Lauriola P, Calzolari E, Astolfi G et al. 2012. Trihalomethanes, chlorite, chlorate in drinking water and risk of congenital anomalies: A population-based case-control study in Northern Italy. *Environ Res* 116:66-73.
- Rogers VV, Wickstrom M, Liber K, MacKinnon MD. 2002. Acute and subchronic mammalian toxicity of naphthenic acids from oil sands tailings. *Toxicol Sci* 66:347-355.
- Sato M, Takigami H, Hayakawa K, Sakai S. 2010. Water-quality monitoring technique for dioxins during dredging using on-site solid phase extraction with graphitic carbon and analysis with DR-CALUX. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 45:867-874.

- Savitz DA. 2012. Invited commentary: biomarkers of exposure to drinking water disinfection by-products--are we ready yet? *Am J Epidemiol* 175:276-278.
- Schreurs RH, Legler J, Artola-Garicano E, Sinnige TL, Lanser PH, Seinen W et al. 2004. In vitro and in vivo antiestrogenic effects of polycyclic musks in zebrafish. *Environ Sci Technol* 38:997-1002.
- Schriks M, Heringa MB, van der Kooi MM, de Voogt P, van Wezel AP. 2010. Toxicological relevance of emerging contaminants for drinking water quality. *Water Res* 44:461-476.
- Schwarzenbach RP, Escher BI, Fenner K, Hofstetter TB, Johnson CA, von Gunten U et al. 2006. The challenge of micropollutants in aquatic systems. *Science* 313:1072-1077.
- Shen R, Andrews SA. 2011. Demonstration of 20 pharmaceuticals and personal care products (PPCPs) as nitrosamine precursors during chloramine disinfection. *Water Res* 45:944-952.
- Silva E, Rajapakse N, Kortenkamp A. 2002. Something from "nothing"--eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environ Sci Technol* 36:1751-1756.
- Smith AH, Lopipero PA, Bates MN, Steinmaus CM. 2002. Public health. Arsenic epidemiology and drinking water standards. *Science* 296:2145-2146.
- Ternes T. 2007. The occurrence of micropollutants in the aquatic environment: a new challenge for water management. *Water Sci Technol* 55:327-332.
- Thompson T, Fawell J, Kunikane S, Darryl Jackson D, Appleyard S, Callan P, et al.: 2007, Chemical safety of drinking-water: Assessing priorities for risk management, Geneva. Available: http://whqlibdoc.who.int/publications/2007/9789241546768_eng.pdf [accessed 26 July 2013]
- Toledano MB, Nieuwenhuijsen MJ, Best N, Whitaker H, Hambly P, de Hoogh C et al. 2005. Relation of trihalomethane concentrations in public water supplies to stillbirth and birth weight in three water regions in England. *Environ Health Perspect* 113:225-232.
- UNICEF and WHO (World Health Organization). 2011. Drinking Water Equity, Safety and Sustainability: Thematic report on drinking water 2011. Available: http://www.wssinfo.org/fileadmin/user_upload/resources/report_wash_low.pdf [accessed 26 July 2013]

- US EPA (United States Environmental Protection Agency). 2009. National Primary Drinking Water Regulations. Available: <http://water.epa.gov/drink/contaminants/upload/mcl-2.pdf> [accessed 23 July 2013]
- Valcarcel Y, Martinez F, Gonzalez-Alonso S, Segura Y, Catala M, Molina R et al. 2012. Drugs of abuse in surface and tap waters of the Tagus River basin: heterogeneous photo-Fenton process is effective in their degradation. *Environ Int* 41:35-43.
- Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr., Lee DH et al. 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev* 33:378-455.
- Villanueva CM, Cantor KP, Cordier S, Jaakkola JJ, King WD, Lynch CF et al. 2004. Disinfection byproducts and bladder cancer. A pooled analysis. *Epidemiology* 15:357-367.
- Villanueva CM, Castano-Vinyals G, Moreno V, Carrasco-Turigas G, Aragonés N, Boldo E et al. 2012. Concentrations and correlations of disinfection by-products in municipal drinking water from an exposure assessment perspective. *Environ Res* 114:1-11.
- Villanueva CM, Silverman DT, Malats N, Tardon A, Garcia-Closas R, Serra C et al. 2009. Determinants of quality of interview and impact on risk estimates in a case-control study of bladder cancer. *Am J Epidemiol* 170:237-243.
- Waller K, Swan SH, Windham GC, Fenster L. 2001. Influence of exposure assessment methods on risk estimates in an epidemiologic study of total trihalomethane exposure and spontaneous abortion. *J Expo Anal Environ Epidemiol* 11:522-531.
- Ward MH, deKok TM, Levallois P, Brender J, Gulis G, Nolan BT et al. 2005. Workgroup report: Drinking-water nitrate and health--recent findings and research needs. *Environ Health Perspect* 113:1607-1614.
- Webb S, Ternes T, Gibert M, Olejniczak K. 2003. Indirect human exposure to pharmaceuticals via drinking water. *Toxicol Lett* 142:157-167.
- WHO (World Health Organization). 2012. Pharmaceuticals in drinking water. Available: http://www.who.int/water_sanitation_health/publications/2012/pharmaceuticals/en/ [accessed 23 July 2013]
- WHO (World Health Organization). 2011 Guidelines for Drinking-water Quality. 4th Edition. Available: http://www.who.int/water_sanitation_health/publications/2011/dwq_chapters/en/ [accessed 23 July 2013]

- Wilbers GJ, Zwolsman G, Klaver G, Hendriks AJ. 2009. Effects of a drought period on physico-chemical surface water quality in a regional catchment area. *J Environ Monit* 11:1298-1302.
- Wild CP. 2005. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 14:1847-1850.
- Wilkins JR, Comstock GW. 1981. Source of drinking water at home and site-specific cancer incidence in Washington County, Maryland. *Am J Epidemiol* 114:178-190.
- Wright JM, Bateson TF. 2004. A sensitivity analysis of bias in relative risk estimates due to disinfection by-product exposure misclassification. *J Expo Anal Environ Epidemiol* 15:212-216.
- Zoni S, Lucchini RG. 2013. Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings. *Curr Opin Pediatr* 25:255-260.
- Zwolsman JJ, van Bokhoven AJ. 2007. Impact of summer droughts on water quality of the Rhine River - a preview of climate change? *Water Sci Technol* 56:45-55.

Table 1. Regulatory limits for chemicals in drinking water by the US EPA, the EU and guidelines by the WHO. Units are expressed in micrograms/liter (except for asbestos).

Chemical	WHO 2011	USEPA 2009	EU 1998	Chemical Group
Acrylamide	0.5	^a	0.1	Organic
Alachlor	20	2	-	Organic
Aldicarb	10	-	-	Organic
Aldrin + dieldrin	0.03	-	-	Organic
Antimony	20	6	5.0	Inorganic
Arsenic	10	10	10	Inorganic
Asbestos (fibers >10 micrometers)	-	7 million fibers/l	-	Inorganic
Atrazine	100 ^b	3	-	Organic
Barium	700	2000	-	Inorganic
Benzene	10	5	1.0	Organic
Benzo(a)pyrene	0.7	0.2	0.010	Organic
Beryllium	-	4	-	Inorganic
Boron	2400	-	1000	Inorganic
Bromate	10	10	10	DBP
Bromodichloromethane	60	-	-	DBP
Bromoform	100	-	-	DBP
Cadmium	3	5	5.0	Inorganic
Carbofuran	7	40	-	Organic
Carbon tetrachloride	4	5	-	Organic
Chloramines (as Cl ₂)	-	4000	-	Disinfectant
Chlorate	700	-	-	DBP
Chlordane	0.2	2	-	Organic
Chlorine	5000	4000	-	Disinfectant
Chlorine dioxide	-	800	-	Disinfectant
Chlorite	700	1000	-	DBP
Chlorobenzene	-	100	-	Organic
Chloroform	300	-	-	DBP
Chlorotoluron	30	-	-	Organic
Chlorpyrifos	30	-	-	Organic
Chromium (total)	50	100	50	Inorganic
Copper	2000	13000	2000	Inorganic
Cyanazine	0.6	-	-	Organic
Cyanide	-	200	50	Inorganic
2,4-D (dichlorophenoxyacetic acid)	30	70	-	Organic
Dalapon	-	200	-	Organic
2,4-DB (dichlorofenoxybutyric acid)	90	-	-	Organic
DDT and metabolites	1	-	-	Organic
Dibromochloromethane	100	-	-	DBP

Chemical	WHO 2011	USEPA 2009	EU 1998	Chemical Group
1,2-Dibromo-3-chloropropane (DBCP)	1	0.2	-	Organic
1,2-Dibromoethane	0.4	-	-	Organic
Dichloroacetate	50	-	-	DBP
Dichloroacetonitrile	20	-	-	DBP
1,2-Dichlorobenzene (o-Dichlorobenzene)	1000	600	-	Organic
1,4-Dichlorobenzene (p-Dichlorobenzene)	300	75	-	Organic
1,2-Dichloroethane	30	5	3.0	Organic
1,2-Dichloroethene	50	-	-	Organic
1,1-Dichloroethylene	-	7	-	Organic
cis-1,2-Dichloroethylene	-	70	-	Organic
trans-1,2-Dichloroethylene	-	100	-	Organic
Dichloromethane	20	5	-	Organic
1,2-Dichloropropane	40	5	-	Organic
1,3-Dichloropropene	20	-	-	Organic
Dichlorprop	100	-	-	Organic
Di(2-ethylhexyl)adipate	-	400	-	Organic
Di(2-ethylhexyl)phtalate	8	6	-	Organic
Dimethoate	6	-	-	Organic
Dinoseb	-	7	-	Organic
1,4-Dioxane	50	-	-	Organic
Dioxin (2,3,7,8-TCDD)	-	0.00003	-	Organic
Diquat	-	20	-	Organic
Edetic acid	600	-	-	Organic
Endothall	-	100	-	Organic
Endrin	0.6	2	-	Organic
Epichlorohydrin	0.4	^a	0.10	Organic
Ethylbenzene	300	700	-	Organic
Ethylene dibromide	-	0.05	-	Organic
Fenoprop/Silvex/2,4,5-TP/2-(2,4,5-trichlorophenoxy)propionic acid	9	50	-	Organic
Fluoride	1500	4000	1500	Inorganic
Glyphosate	-	700	-	Organic
Haloacetic acids (HHA5)	-	60	-	DBP
Heptachlor	-	0.4	-	Organic
Heptachlor epoxide	-	0.2	-	Organic
Hexachlorobenzene	-	1	-	Organic
Hexachlorobutadiene	0.6	-	-	Organic
Hexachlorocyclopentadiene	-	50	-	Organic
Hydroxyatrazine	200	-	-	Organic
Isoproturon	9	-	-	Organic
Lead	10	15	10	Inorganic
Lindane	2	0.2	-	Organic

Chemical	WHO 2011	USEPA 2009	EU 1998	Chemical Group
Mecoprop	10	-	-	Organic
Mercury	6	2	1.0	Inorganic
4-(2-Methyl-4-chlorophenoxy) acetic acid (MCPA)	2	-	-	Organic
Methoxychlor	20	40	-	Organic
Metolachlor	10	-	-	Organic
Microcystin-LR	1	-	-	Algal toxin
Molinate	6	-	-	Organic
Monochloramine	3000	-	-	Disinfectant
Monochloroacetate	20	-	-	DBP
Nickel	70	-	20	Inorganic
Nitrate (NO ₃ ⁻)	50000	45000	50000	Inorganic
Nitrilotriacetic acid	200	-	-	Organic
Nitrite (NO ₂ ⁻)	3000	4500	500	Inorganic
N-Nitrosodimethylamine (NDMA)	0.1	-	-	DBP
Oxamyl (Vydate)	-	200	-	Organic
Pendimethalin	20	-	-	Organic
Pentachlorophenol	9	1	-	Organic
Pesticides	-	-	0.10	Organic
Pesticides-total	-	-	0.50	Organic
Picloram	-	500	-	Organic
Polychlorinated biphenils (PCBs)	-	0.5	-	Organic
Polycyclic aromatic hydrocarbons	-	-	0.10	Organic
Selenium	40	50	10	Inorganic
Simazine	2	4	-	Organic
Sodium dichloroisocyanurate	50000/40000 ^c	-	-	Disinfectant
Styrene	20	100	-	Organic
Tertbutylazine	7	-	-	Organic
Tetrachloroethene (tetrachloroethylene)	40	5	-	Organic
Tetrachloroethylene + trichloroethylene	-	-	10	Organic
Thallium	-	2	-	Inorganic
Toluene	700	1000	-	Organic
Toxaphene	-	3	-	Organic
Trichloroacetate	200	-	-	DBP
1,2,4-Trichlorobenzene	-	70	-	Organic
1,1,1-Trichloroethane	-	200	-	Organic
1,1,2-Trichloroethane	-	5	-	Organic
Trichloroethene/Trichloroethylene	20	5	-	Organic
2,4,6-Trichlorophenol	200	-	-	Organic
2,4,5-T (2,4,5-Trichlorophenoxyacetic acid)	9	-	-	Organic
Trifluralin	20	-	-	Organic
Trihalomethanes, Total	-	80	100	DBP

Chemical	WHO 2011	USEPA 2009	EU 1998	Chemical Group
Vinyl chloride	0.3	2	0.50	Organic
Xylenes	500	10000	-	Organic

^aEach water system must certify annually that when it uses acrylamide and/or epichlorohydrin to treat water, the combination of dose and monomer level does not exceed the levels specified, as follows: Acrylamide = 0.05 percent dosed at 1 mg/l (or equivalent); Epichlorohydrin = 0.01 percent dosed at 20 mg/l (or equivalent). ^bIncluding its chloro-s-triazine metabolites. ^c50 as sodium dichloroisocyanurate, 40 as cyanuric acid.

Table 2. Emerging chemical contaminants that may occur in water sources or treated drinking water, with the current state of information regarding their health effects (Adapted from Richardson and Ternes 2011).

Chemical group	Source	Chemicals	Suspected or known health effects
Algal toxins	Produced by algal blooms from an excess of nutrients (in agricultural runoff and wastewater discharges).	Microcystins (e.g., microcystin-LR), nodularins, anatoxins, cylindrospermopsin and saxitoxins	Microcystin-LR is hepatotoxic, genotoxic and carcinogenic (IARC 2010)
Artificial sweeteners	Consumers > urban wastewater > natural waters > drinking water source	Sucralose (Splenda, SucraPlus), acesulfame, saccharin, cyclamate, etc.	Unknown. Sucralose is a persistent chemical in the environment (half life up to several years)
Brominated flame retardants	Used during many years in commercial products like children's sleepwear, foam cushions in chairs, computers, plastics, and electronics. Diet is a source of exposure as some are persistent and accumulate in fish, eggs, milk and meat	Several chemicals classified in different groups such as polybrominated diphenyl ethers (PBDEs), Polybrominated biphenyl (PBB), hexabromocyclododecane (HBCD), etc.	Neurotoxicity and thyroid disruption (Dingemans et al. 2011)
Benzotriazoles	Complexing agents widely used as anticorrosives and for silver protection in dish washing liquids	The two most common forms are benzotriazole and tolytriazole.	Unknown. Soluble in water, resistant to biodegradation and only partly removed in wastewater treatment.
Disinfection by-products	Generated through reaction between organic matter and a disinfectant (e.g., chlorine, chloramine, chlorine dioxide) in the treatment of drinking water and swimming pools	More than 700 compounds identified to-date, which together are estimated to account for ~ 50% of the total organic halogen content	Genotoxic, carcinogenic, reprotoxic.
Ionic liquids	Organic salts with low melting point (< 100°C) promoted as "green chemistry" replacements to traditional solvents in industry. They exhibit some unique properties including tunable viscosity, miscibility, and electrolytic conductivity, which make them useful for many applications, including organic synthesis and catalysis,	The chemical structures typically involve a cationic or anionic polar headgroup with accompanying alkyl side chains. Cationic head groups include imidazolium, pyridinium, pyrrolidinium, morpholinium, piperidium, quinolinium, quaternary ammonium, and quaternary phosphonium moieties; anionic	Different toxicity in animals (Pham et al. 2010). No human studies.

Chemical group	Source	Chemicals	Suspected or known health effects
	production of fuel cells, batteries, coatings, oils, and nanoparticles, as well as other chemical engineering and biotechnology applications.	head groups include tetrafluoroborate (BF ₄ ⁻), hexafluorophosphate (PF ₆ ⁻), bis(trifluoromethylsulfonyl)-imide [(CF ₃ SO ₂) ₂ N ⁻], dicyanamide [(CN) ₂ N ⁻], chloride, and bromide.	
Illicit drugs	Found in surface waters, but generally removed by treatment in water utilities (Huerta-Fontela et al. 2008)	Several, including amphetamine-like compounds, benzodiazepines, cannabinoids, cocaine, lysergic acid diethylamine (LSD), opioids, and metabolites (Valcarcel et al. 2012).	The effect of the mixture is unknown.
Musks	Highly lipophilic chemicals widely used as fragrance additives in many consumer products including perfumes, lotions, sunscreens, deodorants, and laundry detergents.	Several. May have nitroaromatic structures, as in the case of musk xylene (1-tert-butyl-3,5-dimethyl-2,4,6-trinitrobenzene) or musk ketone (4-tert-butyl-2,6-dimethyl-3,5-dinitroacetophenone), or polycyclic structures, as in the case of 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene (AHTN; trade name, tonalide) 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-(g)-2-benzopyran (HHCB; trade name, galaxolide, 4-acetyl-6-tert-butyl-1,1-dimethylindan (ADBI; trade name, celestolide), dihydropentamethylindanone (DPMI; trade name, cashmeran), or 5-acetyl-1,1,2,3,3,6-examethylindan (AHMI, trade name phantolide).	Endocrine disruption according to animal evidence (Schreurs et al. 2004).
Naphthenic acids	Result from petroleum extraction. Occur naturally in crude oil deposits across the world (up to 4% by weight) and in coal.	Complex mixture of alkylsubstituted acyclic and cyclo-aliphatic carboxylic acids that dissolve in water at neutral or alkaline pH and have surfactant-like properties	Liver toxicity in mammals (Rogers et al. 2002). No human studies.
Nanomaterials	Heterogeneous group of chemicals sized 1 to 100 nm, highly stable, strong, conductors and with	Several chemical groups and structures including fullerenes, nanotubes, quantum dots,	Unknown

Chemical group	Source	Chemicals	Suspected or known health effects
	low permeability	metal oxanes, TiO ₂ , nanoparticles, nanosilver and zerovalent iron nanoparticles.	
Perfluorinated compounds (PFCs,)	Used to make stain repellents (such as Teflon), and in the manufacture of paints, adhesives, waxes, polishes, metals, electronics, fire-fighting foams, and caulks, as well as grease proof coatings for packaging. Diet is the main route of exposure, followed by drinking water, house dust and air.	Different types. The most common are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS).	Liver, pancreatic and testicular tumor in animals. Immunotoxicity (DeWitt et al. 2012), thyroid function disruption (Boas et al. 2012; Melzer et al. 2010).
Pesticide transformation products	Result from the hydrolisis, oxidation, biodegradation or photolysis of pesticides. Can be present at higher levels than the parent compound and can be as toxic or more toxic. Diet is a source of exposure	Several, such as alachlor ethanesulfonic acid (ESA), alachlor oxanilic acid (OA), acetochlor ESA, acetochlor OA, metolachlor ESA, metolachlor OA, 3-hydroxycarbofuran, and terbufos sulfone.	Unknown
Pharmaceuticals	Human consumption > excretion > urban wastewater > natural waters > drinking water source	Several chemicals. Includes antidepressants, antiviral drugs, glucocorticoids, antimycotics, antibiotics, beta-blockers, etc.	The effect of the mixture is unknown.
Siloxanes	Used in cosmetics, deodorants, soaps, hair conditioners, hair dyes, car waxes, baby pacifiers, cookware, cleaners, furniture polishes, and water repellent windshield coatings	Cyclic siloxanes, octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), dodecamethylcyclohexasiloxane (D6), and tetradecamethylcycloheptasiloxane (D7) and linear siloxanes.	Unknown
Sunscreens/UV filters	Personal care products > urban wastewater > natural waters > drinking water source. Identified in drinking water (in Barcelona, Spain) with average concentrations up to 295 ng/l (Diaz-Cruz et al. 2012)	Several. The ones identified in drinking water are: Benzophenone-3 (BP3), Octocrylene (OC), 2-ethylhexyl 4-methoxycinnamate (EHMC), 3-(4-methylbenzylidene) camphor (4-MBC), 2-ethylhexyl 4-(dimethylamino) benzoate (OD-PABA)	Unknown

Chemical group	Source	Chemicals	Suspected or known health effects
Single chemicals			
Dioxane	High-production chemical used as a solvent stabilizer in the manufacture and processing of paper, cotton, textile products, automotive coolants, cosmetics, shampoos and as a stabilizer of 1,1,1-trichloroethane (a degreasing agent)	1,4-dioxane. Regulated by EPA (50 mg/l)	Unknown
Perchlorate	Highly stable and soluble chemical used in solid propellants in rockets, missiles, and fireworks, as well as highway flares. Can be found as a contaminant in sodium hypochlorite. Perchlorate can accumulate in plants and have it has been found in biological samples.	Perchlorate	Unknown. Perchlorate can cross the placenta.

Table 3. Challenges of exposure assessment for chemical contaminants in drinking water.

Challenge	Comments
Low exposure levels	Accuracy of analytical measurements in water is particularly important at the low range of exposure. In addition, detailed personal information of water use behavior is convenient.
Chemicals occurring in mixtures	Examples include pharmaceutical residues and disinfection by-products. Depending on the individual constituents of the mixture, chemical-by-chemical exposure assessment may not be feasible or could result in simplistic exposure estimates.
Time-space variability	Repeated measurements and distribution of sampling points covering different water zones is necessary to evaluate geographical and temporal variation during the relevant exposure period.
Long-term exposure windows	Longer exposure periods are likely to result in greater exposure misclassification. In the case of chronic diseases such as cancer, data collection must include accurate location of study participants (residence and workplace) and water use over the duration of an exposure period relevant to disease etiology. Combined with environmental levels, quantitative estimation of exposure can be conducted. An added challenge is the lack of monitoring data.
Lack of monitoring data	This is particularly problematic to evaluate some exposures (such as emerging contaminants) and some outcomes (such as cancer, since historical records are frequently unavailable). More research is needed to develop validated simulation models that can be used to estimate levels and exposure over the relevant time period.
Lack of validated biomarkers of exposure	Currently available validated biomarkers typically reflect recent exposures and thus may not be useful for outcomes with latency periods longer than the half-life of biomarker compound. Exceptions may occur if the time between consecutive exposure events is shorter than the elimination half-life or exposure can be regarded as constant within the relevant time window (such as for trichloroacetic acid).
Multiple exposure routes (ingestion, inhalation, dermal absorption)	Exposure to a number of water contaminants can occur through multiple routes. For example, some by-products of water disinfection (DBPs) can be incorporated through inhalation, dermal absorption and ingestion. For other waterborne contaminants, such as nitrate (at levels in water below 50 mg/l) and per- and polyfluorinated compounds, diet is the main source of exposure (IARC 2010; Ericson Jogsten 2011). For such contaminants, exposure by all plausible routes should be assessed in order to produce the most accurate estimate of disease risk.

Table 4. Evidence of carcinogenicity as concluded by the WHO International Agency for Research on Cancer (IARC) for some chemicals whose main pathway of human exposure is through drinking water.

Agent	Human evidence	Animal evidence	Overall evaluation	IARC monograph
Elements				
Arsenic	Sufficient	Sufficient	1	Volume 100c (2012)
Fluoride	Inadequate	Inadequate	3	Suppl. 7 (1987)
Nitrate	Inadequate	Inadequate/Sufficient ^a	2A ^b	Volume 94 (2010)
Microcystin-LR	Inadequate	Inadequate	2B	Volume 94 (2010)
Disinfection by-products				
Trihalomethanes				
Chloroform	Inadequate	Sufficient	2B	Volume 73 (1999)
Bromodichloromethane	Inadequate	Sufficient	2B	Volume 52 (1991)
Dibromochloromethane	Inadequate	Limited	3	Volume 52 (1991)
Bromoform	Inadequate	Limited	3	Volume 52 (1991)
Haloacetic acids				
Dichloroacetic acid	Inadequate	Sufficient	2B	Volume 106 (In Press)
Trichloroacetic acid	Inadequate	Sufficient	2B	Volume 106 (In Press)
Bromochloroacetic acid	Inadequate	Sufficient	2B	Volume 101 (2012)
Dibromoacetic acid	Inadequate	Sufficient	2B	Volume 101 (2012)
Halogenated acetonitriles				
Bromochloroacetonitrile	No data	Inadequate	3	Volume 52 (1991)
Chloroacetonitrile	No data	Inadequate	3	Volume 52 (1991)
Dibromoacetonitrile	No data	Inadequate	3	Volume 52 (1991)
Dichloroacetonitrile	No data	Inadequate	3	Volume 52 (1991)
Trichloroacetonitrile	No data	Inadequate	3	Volume 52 (1991)
Dibromoacetonitrile	No data	Sufficient	2B	Volume 101 (2012)
Chloral hydrate	Inadequate	Sufficient	2A	Volume 106 (In Press)
MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone)	Inadequate	Limited	2B ^c	Volume 84 (2004)
Bromate (evaluated as potassium bromate)	Inadequate	Sufficient	2B	Volume 73 (1999)
Chlorite (evaluated as sodium chlorite)	No data	Inadequate	3	Volume 52 (1991)
Chlorinated drinking water	Inadequate	Inadequate	3	Volume 52 (1991)

Agent	Human evidence	Animal evidence	Overall evaluation	IARC monograph
Chemicals used in the disinfection of drinking water				
Hypochlorite salts	No data	Inadequate	3	Volume 52 (1991)
Chloramine	Inadequate	Inadequate	3	Volume 84 (2004)

Overall evaluations: Group 1 (the agent is carcinogenic to humans), 2A (the agent is probably carcinogenic to humans), 2B (the agent is possibly carcinogenic to humans), 3 (the agent is not classifiable as to its carcinogenicity to humans).

^aThere is sufficient evidence in experimental animals for the carcinogenicity of nitrite in combination with amines or amides. ^bIngested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans. ^cOther relevant data were used to upgrade the evaluation. [Modified from the General Remarks to Vol. 84].